Complete Summary

GUIDELINE TITLE

Guidelines for the use of antiretroviral agents in pediatric HIV infection.

BIBLIOGRAPHIC SOURCE(S)

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Bethesda (MD): U.S. Department of Health and Human Services; 2005 Nov 3. 96 p. [197 references]

GUIDELINE STATUS

This is the current release of the guideline.

It updates a previous version: Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Bethesda (MD): U.S. Department of Health and Human Services; 2005 Mar 24. 90 p.

The Working Group will revise these guidelines as new data regarding antiretroviral therapy for infected infants, children, and adolescents become available. Status information regarding this guideline is available from the AIDSinfo Web site, telephone (800) 448-0440, fax (301) 519-6616; TTY (888) 480-3739.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references drugs for which important revised regulatory information has been released.

- On October 14, 2003, the U.S. Food and Drug Administration's (FDA) MedWatch Safety program distributed information from the manufacturer (Gilead Sciences, Inc.) of tenofovir disoproxil fumarate (Viread®)about a high rate of early virologic failure and emergence of nucleoside reverse transcriptase inhibitor (NRTI) resistance associated mutations with the use of the drug in a once-daily triple NRTI regimen along with didanosine enteric coated beadlets (Videx EC, Bristol-Myers Squibb), and lamivudine (Epivir, GlaxoSmithKline). Based on these results, Tenofovir DF in combination with didanosine and lamivudine is not recommended when considering a new treatment regimen for therapy-naïve or experienced patients with HIV infection. Patients currently on this regimen should be considered for treatment modification. For more information, visit the FDA Web site.

- On January 19, 2005, the U.S. Food and Drug Administration (FDA) issued a public health advisory about recent safety-related changes to the nevirapine (Viramune®) label and about appropriate use of HIV triple combination therapy containing nevirapine. The Indications and Usage section now recommends against starting nevirapine treatment in women with CD4+cell counts greater than 250 cells/mm^3 unless benefits clearly outweigh risks. This recommendation is based on a higher observed risk of serious liver toxicity in patients with higher CD4 cell counts prior to initiation of therapy. See the FDA Web site for more information.
- On June 30, 2006, Boehringer Ingelheim and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of important new safety information for Aptivus (tipranavir) capsules, co-administered with ritonavir (500mg/200mg), that includes an addition to the drug's Black Box Warning regarding reports of both fatal and non-fatal intracranial hemorrhage (ICH). Boehringer Ingelheim identified 14 reports of intracranial hemorrhage events, including 8 fatalities, in 6,840 HIV-1 infected individuals receiving Aptivus capsules in combination antiretroviral therapy in clinical trials.

  Many of the patients experiencing ICH in the Aptivus clinical development program had other medical conditions (CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension or alcohol abuse) or were receiving concomitant medications, including anticoagulants and antiplatelet agents, that may have caused or contributed to these events.

  No pattern of abnormal coagulation parameters were observed in patients receiving Aptivus in general, or preceding the development of ICH. Routine measurement of coagulation parameters is not currently indicated in the management of patients on Aptivus. An increased risk of ICH was previously observed in patients with advanced HIV-1 disease/AIDS. Further investigations are ongoing to assess the role of Aptivus in ICH. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Human immunodeficiency virus (HIV) infection
- Acquired immunodeficiency syndrome (AIDS)

GUIDELINE CATEGORY

Management
Prevention
Treatment

CLINICAL SPECIALTY

Allergy and Immunology
Family Practice
Infectious Diseases
Internal Medicine
Pediatrics
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Health Plans
Hospitals
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

To update the existing antiretroviral treatment guidelines for children and to provide guidelines for the antiretroviral treatment of human immunodeficiency virus (HIV)-infected infants, children, and adolescents similar to those for HIV-infected adults

TARGET POPULATION

Human immunodeficiency virus (HIV)-infected infants, children, and adolescents in the United States

INTERVENTIONS AND PRACTICES CONSIDERED

Antiretroviral Therapy

1. Intensive family and patient education, training in the administration of prescribed medications and discussion of the importance of adherence to the drug regimen before initiation of new treatment, including frequent patient visits and intensive follow-up

2. Nucleoside analogue reverse transcriptase inhibitors (NRTIs) and nucleotide reverse transcriptase inhibitors (NtRTIs)
    - Abacavir (ABC, Ziagen™)
    - Didanosine (dideoxyinosine, ddI, Videx®)
    - Emtricitabine (FTC, Emtriva™)
    - Lamivudine (3TC, Epivir®, Epivir HBV®)
    - Stavudine (d4T, Zerit®, Zerit XR®)
    - Tenofovir (Viread®)
    - Zalcitabine (ddC, HIVID®)
    - Zidovudine (ZDV, AZT, Retrovir®)
3. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
    - Delavirdine (DLV, Rescriptor®)
    - Efavirenz (DMP-266, EFV, Sustiva™)
    - Nevirapine (NVP, Viramune®)
4. Protease inhibitors (PIs)
    - Amprenavir (APV, Agenerase™)
    - Atazanavir (ATV, Reyataz™)
    - Fosamprenavir (f-APV, Lexiva®)
    - Indinavir (IDV, Crixivan®)
    - Lopinavir/Ritonavir (Kaletra™, ABT 378, LPV/RTV)
    - Nelfinavir (NFV, Viracept®)
    - Ritonavir (RTV, Norvir®)
    - Saquinavir (SQV, Invirase™ hard gel capsule, and Fortovase™ soft gel capsule)
5. Fusion inhibitors
    - Enfuvirtide (Fuzeon™, T-20)

Note: Although these drugs were considered for use in the target population, not all are recommended. Refer to the "Major Recommendations" field for context.

Note: Detailed information regarding issues associated with specific drug choices for changing a failing regimen and potential cross-resistance between various antiretroviral drugs is available elsewhere. Because these issues are similar for all HIV-infected persons (regardless of age) they are not addressed specifically in this guideline.

MAJOR OUTCOMES CONSIDERED

- Virologic response to antiretroviral therapy as measured by human immunodeficiency virus (HIV) ribonucleic acid (RNA) levels and immunologic response as measured by CD4 lymphocyte count/percent
- Disease progression based on virologic (HIV RNA load), immunologic (CD4+ cell count), or clinical (progressive neurodevelopmental deterioration, growth failure) parameters
- Toxicity of antiretroviral therapy
- Emergence of drug resistance
- Mortality rates
- Rates of opportunistic infections and other complications of HIV infection

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review
Review of Published Meta-Analyses

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

To update the 1993 antiretroviral treatment guidelines for children and to provide guidelines for antiretroviral treatment similar to those for human immunodeficiency virus (HIV)-infected adults, the National Pediatric and Family HIV Resource Center (NPHRC), the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH) reconvened the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, consisting of experts caring for HIV-infected children and adolescents, family members of HIV-infected children, and government agency representatives. The Working Group met in June 1996 and again in July 1997 to establish and finalize new guidelines for the treatment of HIV-infected infants, children, and adolescents.

Since 1998, the Working Group has held monthly conference calls to review new data; recommendations for changes to the pediatric treatment guidelines are reviewed by the Working Group and incorporated as appropriate.

Treatment recommendations are based on published and unpublished data regarding the treatment of HIV infection in infants, children, and adults and, when no definitive data were available, the clinical experience of the Working Group members.

Concepts Considered in the Formulation of Pediatric Treatment Guidelines

The following concepts were considered in the formulation of these guidelines:

- Identification of HIV-infected women before or during pregnancy is critical to providing optimal therapy for both infected women and their children and to preventing perinatal transmission. Therefore, prenatal HIV counseling and testing with consent should be the standard of care for all pregnant women in the United States.
- Enrollment of pregnant HIV-infected women; their HIV-exposed newborns; and infected infants, children, and adolescents into clinical trials offers the best means of determining safe and effective therapies.
- Pharmaceutical companies and the federal government should collaborate to ensure that drug formulations suitable for administration to infants and children are available at the time that new agents are being evaluated in adults.
- Although some information regarding the efficacy of antiretroviral drugs for children can be extrapolated from clinical trials involving adults, concurrent clinical trials for children are needed to determine the impact of the drug on specific manifestations of HIV infection in children, including growth, development, and neurologic disease. However, the absence of clinical trials addressing pediatric-specific manifestations of HIV infection does not preclude the use of any approved antiretroviral drug in children, irrespective of labeling notations.
- Management of HIV infection in infants, children, and adolescents is rapidly evolving and becoming increasingly complex; therefore, wherever possible, management of HIV infection in children and adolescents should be directed by a specialist in the treatment of pediatric and adolescent HIV infection. If this is not possible, such experts should be consulted regularly.
- Effective management of the complex and diverse needs of HIV-infected infants, children, adolescents, and their families requires a multidisciplinary team approach that includes physicians, nurses, social workers, psychologists, nutritionists, outreach workers, and pharmacists.
- Determination of HIV RNA and CD4+ T cell levels is essential for monitoring and modifying antiretroviral treatment in infected children and adolescents as well as adults; therefore, assays to measure these variables should be monitored on a regular basis.
- Health care providers considering antiretroviral regimens for children and adolescents should consider certain factors influencing adherence to therapy, including: availability and palatability of pediatric formulations; impact of the medication schedule on quality of life, including number of medications, frequency of administration, ability to coadminister with other prescribed medications, and need to take with or without food; ability of the child's

caregiver or the adolescent to administer complex drug regimens and availability of resources that might be effective in facilitating adherence; and potential for drug interactions.

- The choice of antiretroviral regimens should include consideration of factors associated with possible limitation of future treatment options, including the presence of or potential for the development of antiretroviral resistance. HIV resistance assays have proven useful in guiding initial therapy and in changing failing regimens, but expert clinical interpretation is required.
- Monitoring growth and development is essential for the care of HIV-infected children. Growth failure and neurodevelopmental deterioration may be specific manifestations of HIV infection in children. Nutritional-support therapy is an intervention that affects immune function, quality of life, and bioactivity of antiretroviral drugs.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): The Department of Health and Human Services updated the "Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection" on November 3, 2005. The section on "Available Antiretroviral Drugs" has been updated to include the protease inhibitor tipranavir. The section on drugs "Not Recommended for Initial Therapy in Children" has also been updated, as were Appendix A, "Characteristics of Available Antiretroviral Drugs," Supplement I, "Pediatric Antiretroviral Drug Information," and Supplement III, "Adverse Drug Effects." Finally, Tables 8, 10, and 11 in the original guideline document were updated to reflect new information. The following guidelines reflect the current recommendations.

Initiation of Antiretroviral Therapy

When to Initiate Therapy

A number of factors need to be considered in making decisions about initiating antiretroviral therapy in children, including:

- Severity of human immunodeficiency virus (HIV) disease and risk of disease progression as determined by presence or history of HIV-related serious or acquired immunodeficiency syndrome (AIDS)-defining illnesses, and the child's CD4+ cell count and plasma HIV ribonucleic acid (RNA) level
- Availability of appropriate (and palatable) drug formulations for the child and pharmacokinetic information on appropriate dosing in the child's age group
- Potency, complexity (e.g., dosing frequency, food and fluid requirements), and potential short- and long-term adverse effects of the antiretroviral regimen
- Effect of initial regimen choice on later therapeutic options
- Presence of comorbidity that could affect drug choice, such as tuberculosis, hepatitis B or C infection, or chronic renal or liver disease (for example, coadministration of rifampin can significantly reduce drug levels of nevirapine* [See note at the end of the "Major Recommendations" field.] and most protease inhibitors; viral hepatitis can predispose to hepatic toxicity of nucleoside and non-nucleoside antiretroviral drugs; and, depending upon the route of metabolism/excretion for individual drugs, dose modification may be required for individuals with significant renal/liver disease)
- Potential antiretroviral drug interactions with other medications required by the child
- The ability of the caregiver and child to adhere to the regimen

Issues associated with adherence to treatment are especially important in considering whether and when to initiate therapy. Antiretroviral therapy is likely to be most effective in patients who are naïve to treatment and who therefore are less likely to have antiretroviral-resistant viral strains. Lack of adherence to prescribed regimens and subtherapeutic levels of antiretroviral medications, particularly protease inhibitors, may enhance the development of drug resistance and likelihood of virologic failure. Participation by the caregivers and child in the decision-making process is crucial, especially in situations for which definitive data concerning efficacy are not available. Issues related to adherence to therapy should be fully assessed, discussed, and addressed with the child´s caregiver and the child (when age-appropriate) before the decision to initiate therapy is made. Potential problems should be identified and resolved prior to starting therapy, even if this delays initiation of therapy. Additionally, frequent follow-up is important to provide assessment of virologic response to therapy, drug intolerance, viral resistance, and adherence.

The choice whether to start therapy early, while an individual is still asymptomatic, versus delaying therapy until clinical or immunologic symptoms appear, continues to generate considerable controversy among pediatric and adult HIV experts. Some experts favor starting aggressive therapy in the early stages of HIV infection in the hope that early antiretroviral intervention will control viral replication prior to the onset of rapid genetic mutation and evolution into multiple quasispecies. This could result in a lower viral "set point," fewer mutant viral strains, and potentially less drug resistance. Early therapy would slow immune system destruction and preserve immune function, preventing clinical disease progression. On the other hand, delaying therapy until later in the course of HIV infection, when clinical or immunologic symptoms appear, may result in reduced

evolution of drug-resistant virus due to a lack of drug selection pressure, greater adherence to the therapeutic regimen when the patient is symptomatic rather than asymptomatic, and reduced or delayed adverse effects of antiretroviral therapy.

Guidelines for initiation of therapy in adults have become more conservative over time; treatment is currently recommended for adults with AIDS or severe symptoms, and for asymptomatic adults with CD4+ cell count $\leq$200/mm^3. The adult guidelines suggest that treatment be considered for individuals with CD4+ cell count between 200-350/mm^3 or plasma HIV RNA levels $\geq$55,000 copies/mL, while therapy could be deferred in individuals with CD4+ cell count >350/mm^3 and plasma HIV RNA levels <55,000 copies/mL. Because HIV disease progression in children is more rapid than in adults, and laboratory parameters are less predictive of risk for disease progression, particularly for young infants, treatment recommendations have been more aggressive in children than in adults.

HIV-Infected Infants Under Age 12 Months

While there is agreement among pediatric HIV experts that infected infants with clinical symptoms of HIV disease or with evidence of immune compromise should be treated, there remains controversy regarding treatment of asymptomatic infants with normal immunologic status. The Working Group recommends initiation of therapy for infants under age 12 months who have clinical or immunologic symptoms of HIV disease, regardless of HIV RNA level, and consideration of therapy for HIV-infected infants under age 12 months who are asymptomatic and have normal immune parameters. Because of the high risk for rapid progression of HIV disease, many experts would treat all HIV-infected infants <12 months old, regardless of clinical, immunologic, or virologic parameters. Other experts would treat all infected infants <6 months old, and use clinical and immunologic parameters and assessment of adherence issues for decisions regarding initiation of therapy in infants 6 to 12 months of age. Some intriguing data suggest that the risk of disease progression during the first 2 years of life may be related to maternal clinical, immunologic, and virologic HIV disease status during pregnancy, with more rapid progression in infants born to women with more advanced HIV disease.

Refer to the original guideline document for a detailed discussion.

HIV-Infected Children Aged 12 Months or Older

The Working Group recommends that treatment should be started for all children over age 12 months with AIDS (Clinical Category C) or severe immune suppression (Immune Category 3), and be considered for children who have mild-moderate clinical symptoms (Clinical Categories A or B), moderate immunologic suppression (Immune Category 2), and/or confirmed plasma HIV RNA levels $\geq$100,000 copies/mL. Many experts would defer treatment in asymptomatic children aged $\geq$1 year with normal immune status in situations in which the risk for clinical disease progression is low (e.g., HIV RNA <100,000 copies/mL) and when other factors (i.e., concern for adherence, safety, and persistence of antiretroviral response) favor postponing treatment. In such cases, the health care provider should closely monitor virologic, immunologic, and clinical status.

Factors to be considered in deciding when to initiate therapy in such children include:

a. Increasing HIV RNA levels (e.g., HIV RNA levels approaching 100,000 copies/mL)
b. Rapidly declining CD4+ T cell count or percentage to values approaching those indicative of severe immune suppression (i.e., Immune Category 3; see Table 1 in the original guideline document)
c. Development of clinical symptoms
d. Ability of caregiver and child to adhere to the prescribed regimen

Choice of Initial Antiretroviral Therapy

Combination therapy is recommended for all infants, children, and adolescents who are treated with antiretroviral agents. When compared with monotherapy, combination therapy slows disease progression and improves survival, results in a greater and more sustained virologic and immunologic response, and delays development of virus mutations which confer resistance to the drugs being used.

Monotherapy with the currently available antiretroviral drugs is no longer recommended to treat HIV infection. Use of zidovudine (ZDV) as a single agent is appropriate only when used in infants of indeterminate HIV status during the first 6 weeks of life to prevent perinatal HIV transmission. Infants who are confirmed as being HIV-infected while receiving ZDV chemoprophylaxis should be changed to a recommended standard combination antiretroviral drug regimen or, if immediate treatment is deferred, ZDV should be discontinued pending therapeutic decisions.

Aggressive antiretroviral therapy with at least three drugs is recommended for initial treatment of infected children because it provides the best opportunity to preserve immune function and delay disease progression. The goal of antiretroviral therapy is to maximally suppress viral replication, preferably to undetectable levels for as long a time as possible, while preserving and/or restoring immune function and minimizing drug toxicity.

New drug combinations that demonstrate sustainable viral load suppression and acceptable toxicity and dosing profiles most likely will become available, and will increase treatment options for children in the future. Since antiretroviral therapy will need to be administered for many years, considerations related to the choice of initial antiretroviral regimen should include an understanding of barriers to adherence, including the complexity of schedules and food requirements for different regimens, as well as palatability problems and potential limitations in subsequent treatment options should resistance develop.

The initial antiretroviral regimen chosen for infected infants theoretically could be influenced by the antiretroviral regimen their mother may have received during pregnancy. However, data from Pediatric AIDS Clinical Trials Group (PACTG) protocol 076 indicate that ZDV resistance did not account for most infants who became infected despite maternal ZDV treatment, and data from Pediatric AIDS Clinical Trials Group protocol 185 indicate that duration of prior ZDV therapy in women with advanced HIV disease, many of whom received prolonged ZDV before pregnancy, was not associated with diminished ZDV efficacy for reduction of

transmission. Data do not suggest that the antiretroviral regimen for infected infants should routinely be chosen on the basis of maternal antiretroviral use.

However, continuing to monitor the frequency of antiretroviral-resistant virus among newly infected infants is important. In a retrospective study of the prevalence of antiretroviral drug resistance in a cohort of 91 HIV-infected infants born in 1998 and 1999 in New York State, 11 (12%) infants had provirus with mutations associated with drug resistance; 2% had resistance to drugs in 2 different drug classes. History of maternal antiretroviral therapy and infant antiretroviral prophylaxis was not significantly associated with the detection of genotypic resistance in infant virus. However, all six infants with both resistance and perinatal antiretroviral exposure had at least one genotypic mutation conferring resistance to an antiretroviral drug they been exposed to; three of these infants had only intrapartum/neonatal drug exposure. The prevalence of drug resistance among this cohort is similar to the 12% to 13% observed among recently infected adults in North America; in adults with acute HIV infection, consideration of resistance testing prior to initiation of therapy is recommended.

The Working Group recommends consideration of resistance testing prior to initiation of therapy in newly diagnosed infants under age 12 months, particularly if the mother has known or suspected infection with drug-resistant virus. There are no definitive data that demonstrate that resistance testing in this setting correlates with greater success of initial antiretroviral therapy, however.

Available Antiretroviral Drugs

As of October 2005, there were 21 antiretroviral drugs approved for use in HIV-infected adults and adolescents; 13 of these have an approved pediatric treatment indication. These drugs fall into several major classes: nucleoside analogue or nucleotide reverse transcriptase inhibitors (NRTIs, NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, and fusion inhibitors. Brief information on drug formulation, pediatric dosing, and toxicity for the individual drugs can be found in the Appendix of the original guideline document: "Characteristics of Available Antiretroviral Drugs". For more detailed discussion of major classes of antiretroviral drugs and individual drugs for treatment of pediatric HIV infection, go to the companion document of the original guideline, Pediatric Antiretroviral Drug Information. The advantages and disadvantages of individual drugs for children are presented in Tables 8-10 in the original guideline document.

Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs)

The nucleoside analogue reverse transcriptase inhibitors (NRTIs) were the first class of antiretroviral drugs that became available for treatment of HIV infection. These drugs include zidovudine (ZDV), didanosine (ddI), lamivudine (3TC), stavudine (d4T), zalcitabine (ddC), abacavir (ABC), and emtricitabine (FTC). All except ddC and FTC are available in liquid formulations. Additionally, two fixed-dose drug combination preparations are available in solid formulations--a fixed-dose combination of ZDV/3TC (Combivir) and a fixed-dose formulation of ZDV/3TC/ABC (Trizivir). These latter two drug formulations are approved for use in adolescents and adults but are not recommended for use in children less then 12 years old for which the adult dosage may not be appropriate.

Dual NRTI combinations form the "backbone" of highly active antiretroviral therapy (HAART) regimens for both adults and children. Dual NRTI combinations that have been studied in children include ZDV and ddI; ZDV and 3TC; d4T and ddI; d4T and 3TC; ZDV and ddC; and ABC in combination with ZDV, 3TC, d4T, or ddI. The choice of specific dual NRTI combinations for children is based upon the:

- Extent of pediatric experience with the specific drug combination
- Potency of the NRTI combination
- Availability of pediatric formulations
- Potential drug interactions
- Short- and long-term toxicity

The most experience in children is with combination ZDV/3TC, ZDV/ddI, and d4T/3TC, which are the Strongly Recommended dual NRTI combinations for inclusion in initial therapy regimens in children. Alternative dual NRTI combinations include ZDV/ABC, 3TC/ABC, and ddI/3TC. ABC-containing regimens have been shown to be as or possibly more potent than ZDV/3TC, but have the potential for ABC-associated life-threatening hypersensitivity reactions in a small proportion of patients. Thus, ABC-containing regimens are listed as Alternative rather than as Strongly Recommended dual NRTI combinations for inclusion in initial therapy regimens in children. While the dual NRTI combination of ddI/3TC has been well tolerated, there is less pediatric experience with ddI/3TC than the preferred regimens, and it is thus recommended as an Alternative as well.

The dual NRTI combinations d4T/ddI and ZDV/ddC are recommended for Use in Special Circumstances. In small pediatric studies, d4T/ddI has been shown to have virologic efficacy and was well tolerated. However, in studies in adults, d4T/ddI-based combination regimens were associated with greater rates of neurotoxicity, hyperlactatemia and lactic acidosis, and lipodystrophy than therapies based on ZDV/3TC; additionally, cases of fatal and non-fatal lactic acidosis with pancreatitis/hepatic steatosis have been reported in women receiving this combination during pregnancy. ZDV/ddC has been studied in children, but ddC is less potent than the other NRTI drugs and has greater toxicity, and thus would not be first choice for inclusion in an initial therapy regimen.

Certain dual NRTI drug combinations are Not Recommended. These include ZDV and d4T, due to pharmacologic interactions that can result in potential virologic antagonism, and dual regimens combining ddC with ddI, d4T, or 3TC, as pediatric experience with these combinations is limited and there is overlapping neurotoxicity between the drugs. FTC was recently approved for use in children over age 3 months. However, data are limited on its use as a component of a dual NRTI combination as initial therapy in children. Therefore, there are Insufficient Data to Recommend use of FTC for initial therapy in children. FTC should not be used in combination with 3TC because the drug structure is similar and the same single resistance mutation (M184V) induces resistance to both drugs.

Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)

Tenofovir disoproxil fumarate is a nucleotide analogue; like the nucleoside analogue reverse transcriptase inhibitor (NRTI) drugs, tenofovir inhibits HIV reverse transcriptase. However, because the drug already possesses a phosphate

molecule, it bypasses the rate-limiting initial phosphorylation step required for activation of NRTIs. Tenofovir was approved for use in combination with other antiretroviral agents for treatment of adults in October 2001; it is not approved for use in pediatric patients <18 years old. The drug is currently in phase I/II studies in the pediatric population, and an oral suspension formulation is under study. However, animal toxicology studies have demonstrated a potential for bone and renal toxicity. Preliminary data from pediatric phase I studies indicate that decreased bone mineral density as measured by dual-energy x-ray absorptiometry (DEXA) scans has been observed in some children. Thus, there are Insufficient Data to Recommended use of this drug for initial therapy in infected children. Given the potential for bone toxicity, the drug may have greater utility for treatment of children in whom other antiretroviral drugs have failed than for initial therapy of treatment naïve children. Additionally, a recent study in antiretroviral-naïve adults found sub-optimal early virologic response to a regimen containing tenofovir in combination with 3TC and ABC, and this combination regimen should not be used for initial treatment of therapy-naïve adults or children.

Non-Nucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)

There are currently three non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) approved for treatment of HIV infection: nevirapine, efavirenz, and delavirdine. Nevirapine has a liquid formulation and is approved for pediatric use in children aged 2 months or older. The capsule formulation of efavirenz is approved for use in children over 3 years of age; a liquid formulation is under study and is available through an expanded access program. Delavirdine is only available in a tablet preparation and is not approved for use in children. The NNRTI class of drugs rapidly reduces viral load; however, drug resistance develops quickly after initiation of monotherapy or with combination therapy that does not fully suppress viral replication, and cross-resistance between drugs in this class is common. Thus, NNRTI drugs should only be used in the context of a HAART regimen, and never as mono- or dual therapy (with the exception of single-dose nevirapine prophylaxis to reduce mother-to-child HIV transmission).

Efavirenz is the Strongly Recommended NNRTI for use in a combination regimen for initial treatment of children over age 3 years who can swallow capsules. Efavirenz in combination with one or two nucleoside analogue reverse transcriptase inhibitors (NRTIs) plus nelfinavir has been shown to produce sustained and durable viral suppression in a large proportion of treated children. Although there are not data in children, a protease inhibitor-sparing regimen of efavirenz plus two NRTIs has had similar efficacy in infected adults. Based on these adult data, the latter protease inhibitor-sparing combination offers an alternative to children when issues of adherence or use of protease inhibitors are problematic. There are currently no pharmacokinetic data available on appropriate dosage of efavirenz in children under age 3 years. A liquid preparation has been studied in children over age 3 years and is available by expanded access, but only a capsular formulation is currently commercially available. Because efavirenz is currently only available in a capsule, while nevirapine is available in a liquid formulation, for children who require a liquid formulation or who are under age 3 years, nevirapine would be the recommended NNRTI.

For children over age 3 years, nevirapine is Recommended as an Alternative NNRTI for initial therapy. Combination therapy with nevirapine, ZDV, and ddI in a small number of young, antiretroviral therapy-naïve infants was associated with substantial and sustained viral suppression in some of the infants. Treatment of therapy-naïve adults with nevirapine plus dual NRTI regimen demonstrated comparable results to triple therapy with the protease inhibitor indinavir, but no similar comparative studies have been performed in children. Results of studies comparing nevirapine-based versus efavirenz-based regimens in adults are conflicting (see Recommendation on Antiretroviral Regimens for Initial Therapy section below) and no comparative studies have been done in children. Because nevirapine therapy is associated with the rare occurrence of significant hypersensitivity reactions, including Stevens-Johnson syndrome, and rare but potentially life-threatening hepatitis, nevirapine is therefore Recommended as an Alternative, as opposed to Strongly Recommended, NNRTI for initial treatment of antiretroviral-naïve children, except for those children under age 3 years or who cannot swallow a capsule.

Since delavirdine has not been studied in or approved for children, there are Insufficient Data to Recommend it for use as initial therapy in children.

Protease Inhibitors

Protease inhibitors with formulations appropriate for infants and children who cannot swallow pills/capsules include nelfinavir, ritonavir, amprenavir, and lopinavir/ritonavir. Nelfinavir is available as a powder formulation that can be mixed with water or food, while the others are available in liquid formulations. Indinavir, saquinavir, atazanavir, tipranavir, and fosamprenavir are only available in capsule and tablet formulations.

Clinical trials involving antiretroviral-naïve children (some as young as 15 days of age) as well as antiretroviral-experienced children provide evidence that the combination of two NRTIs and a protease inhibitor may reduce HIV RNA to undetectable levels in a substantial proportion of children although somewhat less than that observed with similar treatments in infected adults. Nelfinavir, ritonavir, or lopinavir/ritonavir are considered Strongly Recommended protease inhibitors for use in combination with two NRTIs as initial therapy in infected children. These drugs have the greatest clinical experience in the pediatric population, and are available in pediatric formulations.

Indinavir and amprenavir when used in combination with two NRTIs are Recommended as Alternative protease inhibitors for initial therapy due to more limited experience in children, lack of approved liquid dosage formulations, and/or issues of toxicity. The incidence of hematuria and nephrolithiasis with indinavir therapy may be higher in children than adults. Amprenavir should not be used in children <4 years of age because of the lack of data for children in this age group, the uncertain impact of extremely high levels of vitamin E found in the liquid formulation (46 IU of vitamin E per mL; the recommended daily dose of vitamin E in children is 10 IU), and the presence of propylene glycol in the oral liquid preparation in a concentration that exceeds World Health Organization (WHO) standards for use in infants.

Atazanavir is approved for use in HIV-infected adults (in adults, atazanavir coadministration with tenofovir requires low-dose ritonavir boosting to achieve adequate atazanavir drug levels). Although atazanavir is under study in children, pharmacokinetic, safety and efficacy data in pediatric patients are not yet available and no pediatric formulation is commercially available; it is likely that coadministration of atazanavir with a low-dose ritonavir boost will be needed to achieve adequate drug levels in children. Therefore, there are Insufficient Data to Recommend use of atazanavir for initial therapy in children.

Fosamprenavir calcium is a prodrug of amprenavir that is approved for use in combination therapy for HIV-infected adults. Pediatric trials are ongoing at this time, but at present there are Insufficient Data to Recommend use of fosamprenavir for initial therapy in children.

Tipranavir was recently approved for use in adult patients who are highly treatment experienced or have HIV-1 strains resistant to multiple protease inhibitors and who have evidence of viral replication. It must be co-administered with ritonavir to exert its therapeutic effect and achieve adequate plasma concentrations. Tipranavir/ritonavir has been associated with clinical hepatitis and hepatic decompensation, including some fatalities. Its use should be limited to patients with limited treatment options. There are no published data on the safety or efficacy of tipranavir/ritonavir in pediatric patients and insufficient pharmacokinetic data to recommend a pediatric dose. There are Insufficient Data to Recommend use of tipranavir for initial therapy in children.

Studies of infected adults have indicated that some drugs that inhibit the cytochrome P450 system, including the protease inhibitor ritonavir, can produce substantial increases in the drug levels of other protease inhibitors. Low-dose, non-therapeutic doses of ritonavir, when combined with saquinavir, amprenavir, indinavir, fosamprenavir, atazanavir, and tipranavir, have been shown to act as a pharmacological "booster" to produce elevated therapeutic plasma concentrations of the second drug. The protease inhibitor fixed-dose combination lopinavir/ritonavir is a preparation that takes advantage of this pharmacokinetic enhancement by using a low dose of ritonavir to produce sustained therapeutic levels of lopinavir. However, while combinations of ritonavir with saquinavir, indinavir, fosamprenavir, atazanavir, tipranavir, or nelfinavir in infected adults have shown evidence of virologic suppression when combined with dual NRTIs, these studies have been predominantly conducted among treatment-experienced adults, and it is unclear whether dual protease inhibitors offer any substantial benefit over a single protease inhibitor for initial therapy of antiretroviral naïve individuals.

In children, available pharmacokinetic data indicate that administration of saquinavir does not consistently result in efficacious plasma levels, possibly due to increased systemic clearance and reduced oral bioavailability. Therefore, saquinavir should not be used as a sole protease inhibitor in combination therapy in children. To achieve adequate drug levels in children, saquinavir must be administered with a second protease inhibitor that inhibits saquinavir metabolism (e.g., ritonavir or nelfinavir); however, there are only limited pediatric data on appropriate dosing for such combinations.

Studies of dual protease inhibitor combinations are ongoing in treatment-experienced children, but complete data are not yet available. Because information on the pharmacokinetics, safety, and efficacy of dual protease inhibitor combinations in children are limited, with the exception of the co-formulated lopinavir/ritonavir, there are Insufficient Data to Recommend use of dual protease inhibitors as a component of initial therapy in children, although such combinations may have utility as a component of secondary treatment regimens for children who have failed initial therapy.

Fusion Inhibitors

A new class of antiretroviral agents called fusion inhibitors inhibit viral binding or fusion to host target cells; enfuvirtide (T-20), the only approved drug in this class, must be administered subcutaneously. Single- and chronic-dosing phase I/II studies of T-20 in combination with other antiretroviral drugs in treatment-experienced children have been completed, and have demonstrated that the drug is safe and has an additive antiviral effect. T-20 was approved in March 2003 for HIV-infected adults and children 6 years or older for use in combination with other antiretroviral drugs in treatment-experienced patients with evidence of HIV replication despite ongoing antiretroviral therapy. There are currently Insufficient Data to Recommend use of T-20 for initial therapy of HIV infection in children.

Recommendations on Antiretroviral Regimens for Initial Therapy (see Table 11 in the original guideline document for details on specific regimens)

There are few randomized, phase III clinical trials of highly active antiretroviral therapy (HAART) among pediatric patients that provide direct comparison of different treatment regimens; most pediatric drug data come from phase I/II safety and pharmacokinetic trials and nonrandomized, open-label studies. Recommendations on the optimal initial therapy for children are continually being modified as new data become available, new therapies or drug formulations are developed, and late toxicities become recognized. Criteria used by the Working Group for recommending specific drugs or regimens include:

- Data demonstrating durable viral suppression, immunologic improvement, and clinical improvement (when such data are available) with the regimen, preferably in children as well as adults
- Incidence and types of drug toxicity with the regimen
- Availability and palatability of formulations appropriate for pediatric use
- Dosing frequency, and food and fluid requirements
- Potential for drug interactions

The most extensive clinical trial data on initial therapy regimens in adults and children are available for three types of regimens based on drug class: protease inhibitor-based (two nucleoside analogue reverse transcriptase inhibitors [NRTIs] plus a protease inhibitor); non-nucleoside analogue reverse transcriptase inhibitors [NNRTI]-based (two NRTIs plus an NNRTI); and NRTI-based (three NRTI drugs). Each class-based regimen has advantages and disadvantages. Protease inhibitor-based regimens, while highly potent, have a high pill burden and palatability challenges in children (see Table 10 in the original guideline document). NNRTI-based regimens are palatable and effective, but a low genetic

barrier to resistance leads to rapid development of drug resistance mutations when therapy does not fully suppress viral replication, and there is cross-resistance among members of this drug class (see Table 9 in the original guideline document). Triple NRTI-based regimens, while sparing of other drug classes, may have lower potency than other regimens (see Table 8 in the original guideline document). As discussed earlier, within each drug class, some drugs may be preferred over other drugs for treatment of children, based on: the extent of pediatric experience; drug formulation, including taste and volume of syrups and pill size and number; storage and food requirements; and short- and long-term toxicity.

Based on clinical, immunological, and virological data from clinical trials in adults and children, antiretroviral drug regimens are listed as:

- Strongly Recommended
- Alternative Recommendation
- Use in Special Circumstances
- Not Recommended
- Insufficient Data to Recommend

Strongly Recommended Regimens for Initial Therapy of Children

Based on clinical trials in infected adults and children, the antiretroviral regimens that are Strongly Recommended for initial therapy in children include the combination of two NRTIs plus one of the Strongly Recommended protease inhibitors, or the combination of two NRTIs plus the NNRTI efavirenz for children over age 3 years or nevirapine for children under age 3 years or who cannot take capsules. The choice of dual NRTI was previously discussed.

Recommended as Alternatives for Initial Therapy of Children

Antiretroviral regimens Recommended as Alternatives for initial therapy include the combination of two NRTIs with the protease inhibitors indinavir or amprenavir (the latter only for children over 4 years of age); the combination of two NRTIs with nevirapine (for children aged 3 years or older); or the triple NRTI combination of zidovudine (ZDV)/lamivudine (3TC)/abacavir (ABC). While each of the alternative regimens has demonstrated evidence of virologic suppression in some children, either experience in the pediatric population is more limited than for the Strongly Recommended regimens, the extent and durability of suppression less well defined in children, and/or the efficacy may not outweigh potential adverse effects, such as drug toxicity (i.e., indinavir or abacavir).

Use in Special Circumstances for Initial Therapy of Children

Dual NRTI therapy alone is recommended for initial therapy only in Special Circumstances. Use of a regimen consisting of two NRTIs alone may be considered when the health care provider or guardian/patient has concerns regarding the feasibility of adherence to a more complex drug regimen. It is important to note that drug regimens that do not result in sustained viral suppression, such as a dual NRTI regimen, may result in the development of viral resistance to the drugs being used and cross-resistance to other drugs within the same drug class. Thus,

a dual NRTI regimen would be chosen for initial therapy only under very limited circumstances.

Not Recommended for Initial Therapy of Children

Antiretroviral regimens that are Not Recommended for treatment include monotherapy, certain dual NRTI combinations (ZDV and d4T; zalcitabine [ddC] and ddI, d4T or 3TC), and saquinavir as a sole protease inhibitor (see Table 11 in the original guideline document). These combinations are Not Recommended either because of pharmacological antagonism, potential overlapping toxicities, or inferior virologic response. FTC should not be used in combination with 3TC because the drug structure is similar and the same single resistance mutation (M184V) induces resistance to both drugs. As noted earlier, the appropriate pediatric dose of saquinavir has not been defined, and boosting with a second protease inhibitor (nelfinavir or low-dose ritonavir) is required to produce efficacious plasma drug levels; however, there are currently insufficient data to determine appropriate dosage of such combinations in children.

Insufficient Data for Recommendation for Initial Therapy for Children

There are Insufficient Data to Recommend a number of different antiretroviral drug regimens for initial therapy of antiretroviral naïve children. These include: regimens containing the NNRTI delavirdine, which has not been studied in HIV-infected children and is not available in a liquid formulation; dual protease inhibitor-based regimens (with the exception of lopinavir-ritonavir, a co-formulated preparation), because there are only limited data on appropriate dosing and safety of such regimens; regimens containing agents from 3 drug classes (e.g., NRTI plus NNRTI plus a protease inhibitor), with the exception of efavirenz plus nelfinavir and one or two NRTIs, which has been shown to be effective in HIV-infected children; or regimens containing tenofovir, enfuvirtide, FTC, atazanavir, tipranavir, or fosamprenavir, drugs for which pediatric pharmacokinetic and safety data are not currently available to allow informed recommendations or for which liquid formulations are not available.

Issues Regarding Antiretroviral Dosing in Neonates

See the original guideline document for dosing information.

Changing Antiretroviral Therapy

When to Change Antiretroviral Therapy

Patients taking antiretroviral therapy require careful monitoring for medication adherence, virologic, immunologic, and clinical response, and medication intolerance and toxicity. The following are the major indications warranting the review and possible change in antiretroviral therapy:

a. Failure of the current regimen with evidence of disease progression based on virologic, immunologic, or clinical parameters (see Table 12 in the original guideline document)
b. Toxicity or intolerance to the current regimen

c. Consideration of new data demonstrating that a drug or regimen is superior to the current regimen.

When treatment fails or provides only sub-optimal response, clinicians working with patients and their families need to assess the likely contribution of adherence problems to the failure of the current regimen. Even small lapses in adherence can lead to antiretroviral treatment failure. Directly observed therapy, including inpatient hospitalization, may be necessary to distinguish between inadequate adherence and medication failure.

Issues regarding adherence should be addressed to increase the likelihood of a successful outcome when initiating any new regimen. Intensive family education, training in the administration of prescribed medications, and discussion of the importance of adherence to the drug regimen should be completed before initiation of new treatment. In addition, frequent patient visits and intensive follow-up during the initial months after a new antiretroviral regimen is started are necessary to support and educate the family and to monitor adherence, tolerance, and virologic response to the new regimen.

Virologic Considerations for Changing Therapy

The general virologic principles underlying the use of antiretroviral therapy are similar for all HIV-infected persons. Because HIV RNA monitoring is critical for the management of infected children, Working Group members used the available data, and clinical experience when definitive data were not available, to make the following recommendations. These recommendations may require modification as new information becomes available.

Ideally, antiretroviral therapy should maximally suppress viral replication to undetectable levels using HIV RNA assays. This may not always be achievable in HIV-infected children. Perinatally infected children generally have high HIV RNA levels, and clinical benefit may be observed with decrements in HIV RNA levels that do not result in undetectable levels. However, failure to maximally suppress replication may be associated with increased probability of viral mutations and the emergence of drug resistance. Consideration of the implications of changing regimens and the choice of new drugs should include an acknowledgment of the potential for limiting the patient's future options for potent therapy.

Consensus recommendations have been developed using plasma HIV RNA measurements to guide changes in antiretroviral therapy for HIV-infected adults. Because HIV RNA levels in infants who are perinatally infected are high compared with levels observed when therapy is initiated in most infected adults, the initial virologic response of infected infants and young children to initiation of antiretroviral therapy may take longer than observed in adults. In addition, suppression of HIV RNA to undetectable levels may be achieved less often than has been reported for infected adults despite potent combination therapy with two nucleoside analogue reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI). Therefore, virologic indications for changing therapy in infected children differ slightly from those recommended for infected adults. Adult guidelines should be followed for infected adolescents.

Virologic response should be assessed within 4 weeks after initiating or changing therapy. However, the time required to achieve maximal virologic response to therapy may vary depending on the specific baseline HIV RNA value at the time of starting therapy. After a maximal virologic response is achieved, HIV RNA levels should be measured at least every 3 months to monitor continued response to therapy. At least two measurements (taken 1 week apart) should be performed before considering a change in therapy. Resistance testing is recommended in the setting of persistent or increasing HIV RNA levels.

The following situations may indicate a need for change in therapy in infected children. It should be emphasized that partial non-adherence can explain each of the scenarios listed below and must be addressed prior to making any medication changes.

- Less than a minimally acceptable virologic response after 8 to 12 weeks of therapy.

  For children receiving aggressive antiretroviral therapy, such a response is defined as a less than tenfold (1.0 $\log_{10}$) decrease from baseline HIV RNA levels.

- HIV RNA not suppressed to undetectable levels after 4 to 6 months of antiretroviral therapy.

  Although suppression of HIV RNA to undetectable levels and maintenance for prolonged periods is desirable, some data indicate that suppression is not always achievable. In addition, the number of alternative therapeutic regimens for children is limited. The initial HIV RNA level of the child at the start of therapy and the level achieved with therapy should be considered when contemplating potential drug changes. For example, an immediate change in therapy may not be warranted if there is a sustained 1.5 to 2.0 $\log_{10}$ fall in HIV RNA copy number, even if RNA remains detectable at low levels.

- Repeated detection of HIV RNA in children who initially had undetectable levels in response to antiretroviral therapy.

  Continued observation with more frequent evaluation of HIV RNA levels should be considered if the HIV RNA increase is limited (i.e., <5,000 copies/mL). The presence of repeatedly detectable or increasing RNA levels suggests the development of resistance mutations.

- A reproducible increase in HIV RNA copy number among children who have had a substantial HIV RNA response but still have low levels of detectable HIV RNA.

  Such an increase would warrant a change in therapy if, after achieving a virologic nadir, a greater than threefold (>0.5 $\log_{10}$) increase in copy number is observed in children aged $\geq$2 years. Because of the greater biologic variability in RNA in young children, a change in therapy is warranted when a

greater than fivefold (>0.7 $\log_{10}$) increase is observed for children aged <2 years.

Immunologic Considerations for Changing Therapy

CD4+ T cell count and percentage are independent predictors of disease progression and mortality in HIV-infected children. The association of HIV RNA and CD4+ T cell percentage with long-term mortality risk in HIV-infected children has been evaluated; for each absolute decline of five percentiles in CD4+ T cell percentage at baseline or during follow up, the mortality risk ratio increased by 1.3 (95% CI=1.2-1.5), independent of the child's HIV RNA level. For children with CD4+ T cell percentages of <15% (i.e., those in immune category 3), prognosis also was correlated with the degree of depression of CD4+ T cell percentage (i.e., life expectancy was less for children with CD4+ T cell percentages of <5% compared with children with CD4+ T cell percentages of 10 to 14%) (see Table 3 in the original guideline document).

Before considering changing antiretroviral therapy because of a decline in CD4+ T cell values, a minimum of one repeated measurement of CD4+ T cell values should be obtained at least 1 week after the initial test. The following immunologic indications may warrant a change in antiretroviral therapy for HIV-infected children:

- Change in immune classification (see Table 1 in the original guideline document). However, minimal changes in CD4+ T cell percentile that may result in a change in immune category (i.e., from 26% to 24% or from 16% to 14%) may not be as concerning as a rapid substantial change in CD4+ T cell percentile within the same immune category (i.e., a decrease from 35% to 25%).
- For children with CD4+ T cell percentages of <15% (i.e., those in immune category 3), a persistent decline of 5 percentiles or more in CD4+ T cell percentage (i.e., from 15% to 10% or from 10% to 5%).
- A rapid and substantial decrease in absolute CD4+ T cell count (i.e., a >30% decline in <6 months).

Potent antiretroviral therapy usually increases CD4+ T cell values. Failure of a regimen to improve CD4+ T cell values for patients in immune category 3 should prompt review of the available treatment options and possible change in the antiretroviral regimen.

Clinical Considerations for Changing Therapy

The occurrence of certain clinical events while receiving antiretroviral therapy is evidence of HIV disease progression and/or a poor prognosis for infants and children. The following clinical criteria warrant consideration of a change in antiretroviral therapy:

- Progressive neurodevelopmental deterioration (i.e., the presence of two or more of the following findings documented on repeated assessments: impairment in brain growth, decline of cognitive function documented by psychometric testing, or clinical motor dysfunction). In such cases, the new treatment regimen optimally should include at least one antiretroviral drug

with substantial central nervous system penetration (i.e., zidovudine [ZDV] or nevirapine [NVP], which have cerebrospinal fluid/plasma ratios >0.5).
- Growth failure (i.e., persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation).
- Disease progression (i.e., advancement from one pediatric clinical category to another [see Table 2 in the original guideline document]). Prognosis is poorer as patients' progress to more advanced clinical categories. However, in patients with stable immunologic and virologic parameters, progression from one clinical category to another (i.e., from clinical category A to category B) may not represent an indication to change therapy. For example, development of new opportunistic infections, particularly in patients who had severe immunosuppression at the time therapy was initiated, may not reflect a failure of antiretroviral therapy but persistence of immunologic dysfunction despite adequate antiviral response. Thus, in patients whose disease progression is not associated with neurologic deterioration or growth failure, virologic and immunologic parameters should be considered when deciding whether to change therapy.

Choice of a New Antiretroviral Regimen

The choice of a new antiretroviral regimen is dictated by the indications that warranted the change in therapy (e.g., toxicity/intolerance vs. drug resistance vs. poor adherence) and the available alternative antiretroviral agents. Although the efficacy of different combination antiretroviral regimens in children probably can be extrapolated from clinical trial data obtained for adults, data are limited regarding the pharmacokinetics, appropriate dosing, and short- and long-term safety of various combinations in infected children. A decision to change therapy and the proposed new regimen to be chosen should partly take into account the impact of the changes on future treatment options.

The following principles should be followed when choosing a new antiretroviral regimen in children who have received prior treatment.

- When therapy is changed because of toxicity or intolerance, agents with different toxicity and side-effect profiles should be chosen, when possible. Health care providers should have comprehensive knowledge of the toxicity profile of each agent before selecting a new regimen. In the event of drug intolerance, change of a single drug in a multidrug regimen--and in certain circumstances, dose reduction--are permissible options. Only reduce antiretroviral drug doses to the lower end of the therapeutic range when 1) an effective dosing range is known, 2) drug toxicity is caused by a higher than acceptable drug exposure, and 3) drug levels can be monitored to ensure that plasma concentrations stay within the therapeutic range. While adequacy of antiretroviral activity should be confirmed by monitoring of HIV RNA levels in the period immediately following the regimen change, subtherapeutic dosing may not manifest with sudden increase in viral load, but rather may result in shortened duration of benefit.
- Before changing therapy because of treatment failure (see Table 12 in the original guideline document), adherence to therapy should be assessed to determine what role it played as a potential cause of treatment failure.
- In addition to poor adherence, inadequate drug exposure can occur with inadequate absorption or rapid drug metabolism. Drug exposure may be

enhanced or reduced by administering medications with food. These factors should also be considered as potential contributing factors when a regimen fails. Drug interactions can alter drug metabolism, and all concomitant medications, including over the counter medications and nutritional supplements, should be reviewed to understand whether they might play a role in regimen failure and to make sure appropriate medications and doses are chosen for any new regimens.

- If the patient is adherent to the prescribed drug regimen, assume the development of drug resistance to one or more of the medications in the regimen and perform resistance testing (genotypic or phenotypic) before discontinuing the regimen or initiating a new regimen (see Antiretroviral Drug Resistance Testing below). If possible, change at least two drugs to new antiretroviral agents. A change in one drug or addition of a single drug to a failing regimen is suboptimal. Whenever possible, the new regimen should contain at least three medications with combinations guided by the same decision process used to develop the initial regimen (see Table 11 in the original guideline document). The potential for cross-resistance between antiretroviral drugs should be considered.
- A change to a new regimen, especially one containing protease inhibitors or non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), must include a discussion of treatment adherence issues by the health care provider with the patient, when age-appropriate, and caregivers of the infected child. The health care provider must recognize that certain medications are difficult to take in combination because of exacting and often conflicting requirements with respect to whether they can be taken with food and other antiretrovirals. Palatability, pill size, pill number, and dosing frequency are part of the considerations in choice of new regimen and should be discussed with the child, when appropriate, and the child's caregivers.
- When considering changing to a new regimen, all other medications taken by the patient should be reviewed for possible drug interactions.
- For patients requiring a change of therapy for treatment failure but without treatment options using currently approved drugs, referral to a pediatric HIV specialist for inclusion into a clinical trial should be considered.
- Some studies, primarily in adults, have demonstrated that some patients who are maintained on highly active antiretroviral therapy (HAART) (primarily protease inhibitor-based regimens) may maintain immunologic (e.g. CD4+ cell count) and clinical benefit for up to 3 years despite detectable viral replication. Therefore, in patients who have persistent improvement in CD4+ cell count despite detectable viremia, some clinicians would consider continuation of antiretroviral therapy as long as immunologic benefit was observed. However, sequential development of resistance mutation is noted with increasing time since virologic failure. If appropriate alternative drugs become available, it is usually preferable to change therapy before higher levels of resistance or broad cross-resistance develops. Optimizing a treatment regimen may best be accomplished through consultation with a pediatric HIV specialist.
- When changing therapy because of disease progression in a patient with advanced disease, the patient's quality of life must be considered. Frank discussions of the relative benefits (reduced viral fitness, continued clinical benefit despite resistance, etc.) and burdens of continued antiretroviral therapy should occur. Decisions to continue or discontinue antiretroviral therapy should be made collaboratively with patients, families and health care providers and should be consistent with the patient's/family's stated values

and goals for care. There may be clinical and immunologic benefit in continuing a "failing" regimen because of the decrease in viral fitness associated with continuing therapy despite multiresistant virus and increasing viral load.

- The creation of an effective and sustainable therapeutic regimen may be limited by the availability of potent and/or tolerable therapeutic agents. When deciding whether to change therapy and the contents of a regimen, the clinician should consider the potential availability and future use of newer therapeutic agents that may be in clinical development. Information concerning potential trials can be found at the AIDSinfo Web site or through discussions with a pediatric HIV expert.

Detailed information regarding issues associated with specific drug choices for changing a failing regimen and potential cross-resistance between various antiretroviral drugs is available elsewhere. Because these issues are similar for all HIV-infected persons (regardless of age) they are not addressed specifically in this document.

Antiretroviral Drug Resistance Testing

The optimal goal of antiretroviral therapy is to reduce plasma HIV RNA to below detection of the most sensitive assay available (<50 copies/mL). Accomplishing this level of viral suppression, while not always possible in perinatally infected infants and children, will reduce the likelihood that genotypic (GT)/phenotypic (PT) resistance will emerge.

Several GT assays are available for detecting specific HIV genetic variants (mutations). They are based on amplification procedures and can usually detect mutations in plasma samples with more than 1,000 copies/mL of HIV RNA. A compilation of the most common HIV-1 mutations selected by currently available antiretroviral agents is available at: http://hiv-web.lanl.gov or http://hivdb.stanford.edu.

PT assays directly measure the ability of the viral isolate to grow in the presence of a drug and measure the 50% or 90% inhibitory concentrations of a drug against the virus in vitro, compared to a laboratory strain of wild type virus. The result is expressed as a "fold-change" in susceptibility above a particular cut-off level, below which the virus is assumed to be drug sensitive. These assays have historically been more complex than GT assays but are now available from commercial laboratories.

A method for predicting PT based on the GT is also available. This method matches mutations obtained from the patient sample with a large database of samples for which both genotype and phenotype are known. Thus, the sample is assigned a predicted phenotype susceptibility based on the mean of all the individual samples matching the patient's genotype. The result is expressed as a fold-change. In this assay, both the GT and predicted PT are contained in the test report.

Results of clinical trials with laboratory endpoints in adults have indicated that using genotypic or phenotypic testing to help guide changes in antiretroviral therapy results in a significantly greater, short term, virologic response compared

to clinical judgment alone. Although results of similar trials in children are not available, most pediatric experts do not think viral replication in the face of resistance differs between children and adults.

Therefore, the Working Group recommends the use of resistance assays (either GT or PT) when considering changing antiretroviral therapy because of virologic failure. While there are insufficient pediatric data to recommend use of one type of resistance assay over the other, an individual patient should have one assay used consistently. In children who have complex antiretroviral treatment histories, the use of both assay types (GT and PT) may provide complimentary information that could prove useful in selecting a new regimen.

Resistance assays should be obtained when patients are still on the failing regimen and have a viral load of greater than 1,000 copies/mL. If no resistance to currently used antiretroviral agents is detected in the face of virologic failure, it is likely that the patient is not adhering to the current regimen, and adherence issues should be addressed.

Infected infants born to antiretroviral (ARV)-experienced women may become infected with resistant maternal viral strains. In one early study, only the wild type virus was found in infected infants born to mothers who had a mixed viral population of wild type and low-level zidovudine resistant strains. However, antiretroviral drug resistance in newly infected infants may become more prevalent over time; 12% of HIV-infected infants born in New York in 1998 and 1999 and evaluated for drug resistance within the first 6 months of life had provirus containing resistance mutations. While there are no definitive data that demonstrate that resistance testing correlates with greater success of initial antiretroviral therapy in newly diagnosed infants under age 12 months, the Working Group recommends consideration of resistance testing prior to initiation of therapy in this setting.

The presence of viral resistance to a particular drug suggests that this drug is unlikely to suppress viral replication. However, the absence of resistance to a drug does not insure that its use will be successful, particularly if it shares cross-resistance with drugs previously used. GT or PT assays will detect resistance of the major viral species present, but will not detect resistance in minor viral species constituting less than 10% to 20% of the circulating viral population. Thus, drug resistant virus could still be present at levels below detection with the current assays if resistance developed to an antiretroviral drug previously used, but not part of the child's current regimen. Inability to detect virus is due to the loss of growth advantage of the resistant virus after a specific drug is discontinued. The history of past use of antiretroviral agents is therefore essential in making decisions regarding the choice of new agents for patients with virologic failure. Consultation with a specialist in pediatric HIV infection is recommended for interpretation of resistance assays when considering starting an ARV regimen in infants or changing an antiretroviral regimen in children.

Managing Complications of HIV Infection

The Pediatric Antiretroviral Treatment Guidelines now include the supplements Managing Complications of HIV Infection and Adverse Drug Effects. These supplements contain guidelines for special management issues in pediatric HIV

infection, including pain management and nutrition, as well as separate sections on specific adverse drug effects, including lactic acidosis, hepatic toxicity, fat maldistribution and body habitus changes, hyperlipidemia, hyperglycemia, osteopenia, hematological complications, and hypersensitivity reactions and skin rashes. Earlier versions of these documents were previously included in a companion document to the Pediatric Antiretroviral Treatment Guidelines; this companion document was published as a supplement in Pediatrics in 1998. The Working Group will update the "Managing Complications" supplement to the DHHS Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection with additional sections on management and adverse drug events as needed, or will refer to other pediatric HIV management consensus documents.

The United States Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA) jointly developed and published guidelines for the prevention of opportunistic infection in both children and adults with HIV. These guidelines are available online at the AIDSinfo Web site. (See also the National Guideline Clearinghouse [NGC] summary 2001 USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus). Separate guidelines for the treatment of opportunistic infections in HIV-exposed and infected children have been developed, and will be published and available online in the near future.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Although prospective, randomized, controlled clinical trials offer the best evidence for formulation of guidelines, most antiretroviral drugs are approved for use in pediatric patients based on efficacy data from clinical trials in adults, with supporting pharmacokinetic and safety data from phase I/II trials in children. Additionally, efficacy has been defined in most adult trials based on surrogate marker data, as opposed to clinical endpoints. For the development of these guidelines, the Working Group reviewed relevant clinical trials published in peer-review journals or in abstract form, with attention to data from pediatric populations when available.

Treatment recommendations are based on published and unpublished data regarding the treatment of HIV infection in adults and children and, when no definitive data were available, the clinical experience of the Working Group members.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Effective antiretroviral therapy may reduce human immunodeficiency virus (HIV) viral load to below detection of the most sensitive assay available (<50 copies/mL) and may reduce disease progression and mortality in many infected infants, children and adolescents
- Reduced mortality
- Reduction in opportunistic infections and other complications of HIV infection

Subgroups Most Likely to Benefit

Antiretroviral therapy is likely to be most effective in patients who are naïve to treatment and who therefore are less likely to have antiretroviral-resistant viral strains.

POTENTIAL HARMS

- The possibility of toxicities such as lipodystrophy, dyslipidemia, glucose intolerance, osteopenia, and mitochondrial dysfunction with prolonged therapy is a concern. These concerns are particularly relevant because life-long administration of therapy may be necessary. See the Appendix "Characteristics of Available Antiretroviral Drugs" in the original guideline document and the companion document Adverse Drug Effects for major toxicities and adverse events associated with the antiretroviral drugs.
- Resistance to antiretroviral drugs can develop rapidly (particularly in the setting of high viral replication, as observed in infected infants) when drug concentrations are sub-therapeutic, either because of inadequate dosing, poor absorption, or incomplete adherence.
- Even small lapses in adherence can lead to antiretroviral treatment failure.

CONTRAINDICATIONS

CONTRAINDICATIONS

Please refer to the Appendix "Characteristics of Available Antiretroviral Drugs" in the original guideline document and the companion document Pediatric Antiretroviral Drug Information for a list of contraindicated medications.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The Working Group intends the guidelines to be flexible and not to supplant the clinical judgment of experienced health care providers.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Personal Digital Assistant (PDA) Downloads
Pocket Guide/Reference Cards
Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

RELATED QUALITY TOOLS

- AIDSinfo's Drug Database for Palm PDAs

- AIDSInfo Drug Database

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Bethesda (MD): U.S. Department of Health and Human Services; 2005 Nov 3. 96 p. [197 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Apr (revised 2005 Nov 3)

GUIDELINE DEVELOPER(S)

Centers for Disease Control and Prevention - Federal Government Agency [U.S.]
Health Resources and Services Administration - Federal Government Agency [U.S.]
National Institutes of Health (U.S.) - Federal Government Agency [U.S.]
National Pediatric and Family HIV Resource Center - Private Nonprofit Organization

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United States Government

GUIDELINE COMMITTEE

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children convened by the National Pediatric and Family HIV Resource Center (NPHRC), the Health Resources and Services Administration (HRSA), and the National Institutes of Health (NIH)

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- None

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- Boehringer Ingelheim (Consultant)
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- Hoffman-La Roche Inc. (Research support)
- Pharmasset Pharmaceuticals (Research support)

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American Academy of Pediatrics - Medical Specialty Society

GUIDELINE STATUS

This is the current release of the guideline.

It updates a previous version: Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Bethesda (MD): U.S. Department of Health and Human Services; 2005 Mar 24. 90 p.

The Working Group will revise these guidelines as new data regarding antiretroviral therapy for infected infants, children, and adolescents become available. Status information regarding this guideline is available from the AIDSinfo Web site, telephone (800) 448-0440, fax (301) 519-6616; TTY (888) 480-3739.

GUIDELINE AVAILABILITY

Electronic copies: Available from the AIDSinfo Web site.

The guideline is also available for Palm OS or Pocket PC download from the AIDSinfo Web site.

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012 International number (301)-562-1098. Web site: http://www.cdcnpin.org. Requests for print copies can also be submitted via the AIDSinfo Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Pediatric antiretroviral drug information. Bethesda (MD): Department of Health and Human Services, Public Health Service (PHS), Centers for Disease Control and Prevention (CDC); 2001 Dec 14 (revised 2005 Nov 3). 43 p.

  Electronic copies: Available in Portable Document Format (PDF) from the AIDSinfo Web site. Also available for Palm OS or Pocket PC download from the AIDSinfo Web site.

- Managing complications of HIV infection in HIV-infected children on antiretroviral therapy. Bethesda (MD): Department of Health and Human Services, Public Health Service (PHS), Centers for Disease Control and Prevention (CDC); 2005 Nov 3. 14 p.

  Electronic copies: Available in Portable Document Format (PDF) from the AIDSinfo Web site.

- Adverse drug effects. Bethesda (MD): Department of Health and Human Services, Public Health Service (PHS), Centers for Disease Control and Prevention (CDC); 2005 Nov 3. 30 p.

  Electronic copies: Available in Portable Document Format (PDF) from the AIDSinfo Web site.

- Appendix A: characteristics of available antiretroviral drugs. Bethesda (MD): Department of Health and Human Services, Public Health Service (PHS), Centers for Disease Control and Prevention (CDC); 2001 Dec 14 (revised 2005 Nov 3). 31 p.

  Electronic copies: Available in PDF format from the AIDSinfo Web site.

The following Power Point slide sets based on the "Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection" are also available:

- Pediatric antiretroviral guidelines slide set. AIDS Education and Training Centers (AETC) National Resource Center. 2005 Nov 3. 63 slides. Available from the AETC Web site.

- Pediatric antiretroviral guidelines: pain management. AIDS Education and Training Centers (AETC) National Resource Center. 2005 Mar 24. 25 slides. Available from the AETC Web site.
- Pediatric antiretroviral guidelines: nutritional care. AIDS Education and Training Centers (AETC) National Resource Center. 2005 Mar 24. 20 slides. Available from the AETC Web site.
- Pediatric antiretroviral guidelines: adverse drug effects. AIDS Education and Training Centers (AETC) National Resource Center. 2005 Mar 24. 47 slides. Available from the AETC Web site.

The following tools are also available:

- AIDSinfo's Drug Database for Palm PDAs. Available from the AIDSinfo Web site.
- AIDSinfo's HIV/AIDS Glossary for Palm PDAs, 4th ed. Available from the AIDSinfo Web site in HTML Format, Portable Document Format (PDF), and Spanish.

PATIENT RESOURCES

The following is available:

- HIV during pregnancy, labor and delivery, and after birth. Fact sheets. Rockville (MD): Department of Health and Human Services (DHHS); 2005 May. 9 p.

Electronic copies: Available in Portable Document Format (PDF) from the AIDSinfo Web site.

Print copies: Available from the Centers for Disease Control and Prevention, National Prevention Information Network (NPIN), P.O. Box 6003, Rockville, MD 20850. Telephone: (800) 458-5231, TTY (800)-243-7012 International number (301)-562-1098. Web site: http://www.cdcnpin.org.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on March 27, 1999. The original information was verified by the guideline developer on April 29, 1999. This summary was updated by ECRI on February 15, 2000, August 27, 2001, January 12, 2002, July 1, 2003, October 14, 2003, December 8, 2003, January 22, 2004, and December 1, 2004. This summary was updated on January 21, 2005, following the release of a public health advisory from the U.S. Food and Drug Administration regarding the use of nevirapine. This summary was updated on

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